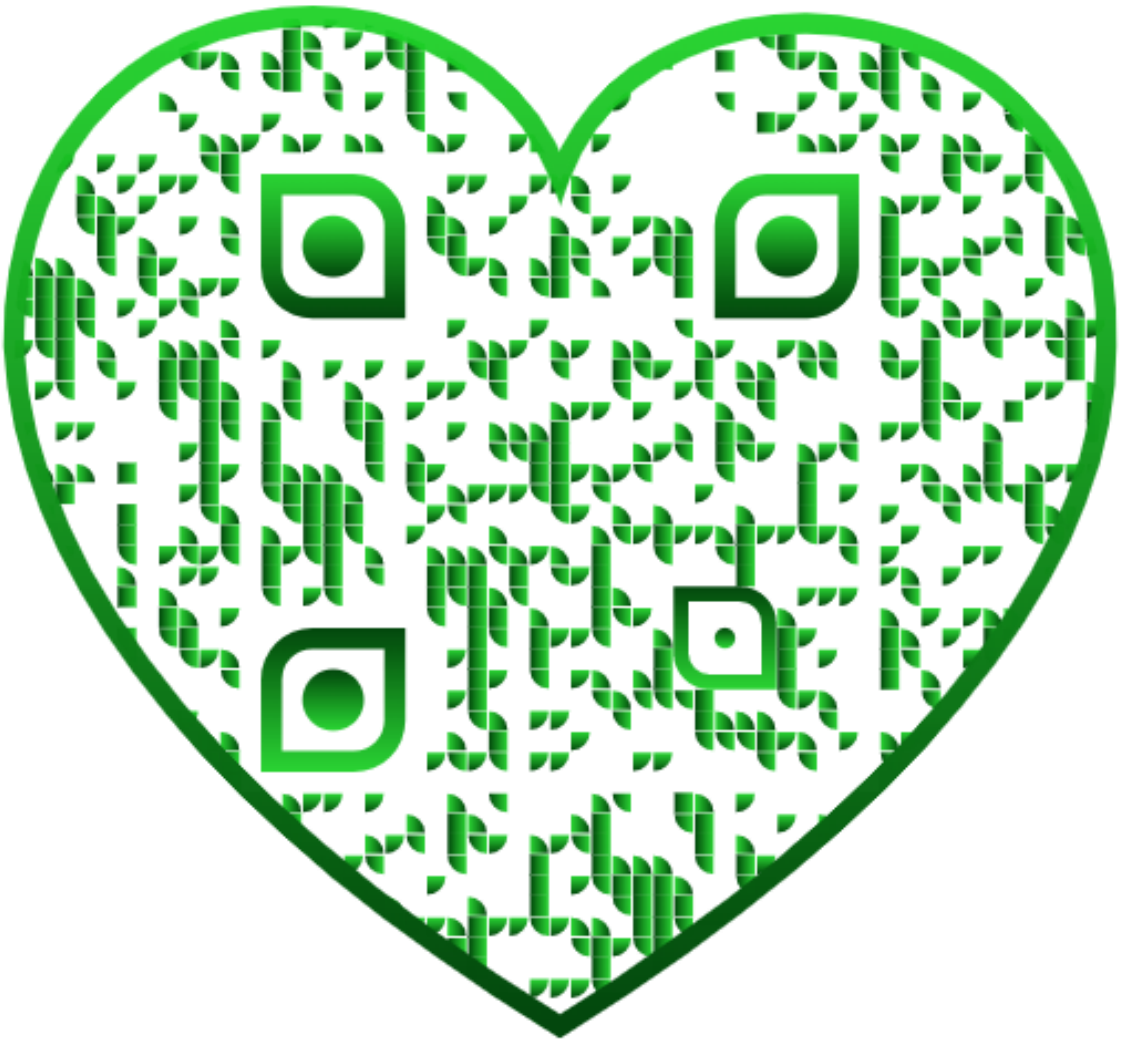
9. Good Manufacturing Practices



Good Manufacturing Practice

Definition

- Good manufacturing practice (GMP) is defined as:
    - "the part of Quality Assurance which ensures that products are **consistently** produced and controlled in accordance with the quality standards appropriate to their **intended use**."
- GMP is a system for ensuring that products are consistently produced and controlled according to quality standards.

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- The first predecessors of manufacturing and quality requirements, which later evolved into GMPs, were issued in the 1940s in the US by the FDA.
- Adopted by WHO in 1969.
- And many countries have passed laws on control procedures essential for the manufacture of drug products.
- Control procedures shall be established to ***monitor*** output and to ***validate*** performance of the manufacturing processes.

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- GMP is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.

- The main risks are:

  - Unexpected contamination of products, causing damage to health or even death;

  - Wrong labels on containers, leading to the patient getting the wrong medicine;

  - Not enough or too much active ingredient, resulting in ineffective treatment or adverse effects.

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- GMP covers all aspects of production; from the starting materials, premises and equipment, to the training and personal hygiene of staff.

- Detailed written procedures are essential for any process that could affect the quality of the finished product.

- There must be systems to provide documented proof that **correct procedures** are **consistently** followed at each step in the manufacturing process - every time a product is made.

Why are GMPs important?

- Poor quality medicines are not only a health hazard, but a waste of money for both governments and individual consumers.
    - A poor quality medicine may contain toxic substances that have been added unintentionally.
    - In Haiti in 1996, more than 80 children died after receiving a cough and cold syrup containing glycerol contaminated with diethylene glycol.
        - If the manufacturer had followed GMP, these deaths could have been avoided.

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- The objective of GMP is to assure the
  - Safety
  - Efficacy and
  - Quality

  of drug products

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- Total Quality Control (TQC) concept
  - The concept includes all control measures contributing for the completed market dosage form
  - Total control of quality is a **plant-wide activity** and represents the aggregate responsibility of all segments of the industry.

GMP basic requirements

- Manufacturing processes are clearly **defined** and **controlled** to ensure consistency and compliance with approved specifications.
- Critical steps of manufacturing processes and significant **changes** to the process are **validated**.
- Instructions and procedures are **written** in clear and unambiguous language.

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- All necessary key elements for GMP are provided, including the following:
    - Qualified and trained personnel,
    - Adequate premises and space,
    - Suitable equipment and services,
    - Correct materials, containers and labels,
    - Approved procedures and instructions,
    - Suitable storage and transport.

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- Operators are trained to carry out and document procedures.
- Records are made that enable the complete history of a lot to be traced are retained in a comprehensible and accessible form.
- Control of storage, handling, and transportation of the drugs minimizes any risk to their quality.
- A system is available for recalling of drugs from sale.
- Complaints about drugs are examined, the causes of quality defects are investigated, and appropriate measures are taken.

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- The GMP requirements were established to be flexible.
    - Each manufacturer is allowed to decide individually how to best implement the necessary controls by using scientifically sound design, processing methods, and testing procedures.
- The flexibility in these regulations allows companies to use **modern** technologies and **innovative** approaches to achieve higher quality through continual improvement.

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- Accordingly, the "c" in cGMP stands for "current," requiring companies to use technologies and systems that are **up-to-date** in order to comply with the regulations.

- Systems and equipment that may have been "top-of-the-line" to prevent contamination, mix-ups, and errors 10 or 20 years ago may be less than adequate by today's standards.

- Compliance with cGMP is not static situation, but requires the manufacturer to be aware not only of what is current in the industry but also to be aware of innovations which may be good.

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- cGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities.

- Adherence to the cGMP regulations assures the identity, strength, quality, and purity of drug products.

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- This requires
  - Establishing strong quality management systems,
  - Obtaining appropriate quality raw materials,
  - Establishing robust operating procedures,
  - Detecting and investigating product quality deviations, and
  - Maintaining reliable testing laboratories.

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- To comply with GMP, holders of manufacturer’s authorizations must:
  - Establish and implement an effective pharmaceutical quality assurance system
  - Have competent and appropriately qualified personnel, sufficient in number to achieve the pharmaceutical quality objective(s)
  - Define the duties of managerial and supervisory staff responsible for implementing and operating GMP in their job descriptions

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- Give personnel sufficient authority and training to meet the pharmaceutical quality objective(s)
- Institute and maintain hygiene programs relating to health, hygiene and clothing;
- Provide and maintain premises and equipment appropriate to the intended operations;
- Have system(s) of documentation covering all the processes and specifications covering the various operations.

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- Provide and maintain an independent quality control department, under the authority of the person nominated as responsible for overall quality control;
- Retain records and samples of starting materials and finished products for the required periods;
- Ensure that any work contracted out is the subject of a written contract;
- Maintain an effective system whereby complaints are reviewed and products may be recalled;
- Carry out a program of regular self-inspections

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- GMP requirements for manufacturers of pharmaceutical dosage forms:

1. Regulations
2. Organization and Personnel
3. Buildings and Facilities
4. Equipment
5. Control of Components and Drug Product Containers and Closures
6. Production and Process Controls
7. Packaging and Labeling Control
8. Holding and Distribution
9. Laboratory Controls
10. Records and Reports
11. Returned and Salvaged Drug Products

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1. Regulations of cGMP

- Documented activities
  - All activities (detailed enough) needs to be documented.
- Validated processes
  - Formulation variables
  - Optimization
  - Process (manufacturing) variables
  - Stability studies
  - Analytical methods

2. Organization and Personnel

Organization

- QC and QA Unit
- Production unit
- Research and development unit
- Personnel

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Responsibilities of QC Unit

- Approve or reject all components, drug product containers closures, in process materials, packaging materials, labelling and drug products;
- Review production records to assure that no errors have occurred, or if errors have occurred, that they have been fully investigated;
- Approve or reject drug products manufactured, processed, packed or held under contract by another company;
- Approve or reject all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product

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- The responsibilities and procedures applicable to the QC Unit shall be in writing, such written procedures shall be followed. cGMPs focus all responsibility for quality onto the QC Unit.

- Approval of standard operating procedures (SOPs) of productions;

- Control of process validation;

- Suppliers certification protocols;

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- Complaint handling;
- Process control procedures;
- Design of buildings;
- Approving or rejecting labelling
- Creation of quality awareness

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Personnel

Personnel qualifications

- Each person engaged in the manufacture or for supervising the manufacture, processing, packaging or holding of drug product shall have education, training, and experience or any combination thereof, to enable that person to perform the assigned functions.

- There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packaging or holding of each drug product.

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Personnel responsibilities

- Personnel engaged in the manufacture, processing, packaging or holding of drug product shall **wear** clean clothing appropriate for the duties they perform.
- Protector apparel – such as head, face, hand and arm **coverage** shall be worn.
- Personnel shall practice good **sanitation** and health habits.
- Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as **limited-access areas**.

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- Any person having an apparent **illness** or open lesions shall be excluded from direct contact with components, containers, closures, in-process materials, packaging materials, labelling and drug products.

- Consultants advising on the manufacture, processing, packing or holding of drug product shall have sufficient education, training, and experience or any combination thereof, to advise on the subject for which they are retained.

- Records shall be maintained stating the name, address and qualification of any consultants and the type of service they provide.

3. Building and Facilities

- Design and construction features
- Lighting
- Heating, ventilation, and air conditioning
- Plumbing
- Sewage and refuse
- Washing and toilet facilities
- Sanitation
- Maintenance

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Design and construction features

- Any building used in the manufacture, processing, packing or holding of drug product shall be of **suitable size**, construction and location to **facilitate cleaning**, **maintenance**, and proper **operations**.

- Two major areas of concern with regard to building and facilities are the External Environment and the Internal Environment.

- Site selection is important.

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Considerations prior to investment

- Adequate space for future expansion.
- Zoning laws to allow anticipated development while restricting undesirable development in the vicinity.
- Availability of water (Quality & Quantity), power, fuel, sewage and waste stream removal.
- Accessibility for employees to public transportation.

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- Environmental issues such as site history, soil, water and air quality and geological and topological issues (potential for flooding, earthquake, foundation instability).
- Proximity to undesirable activities (should be free from source of vermin, insects, odor, MOs, other industries, disposal sites, open mining).
- Availability of suitable labor force.
- Availability to provide adequate security arrangements.

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- Proximity to interrelated operations, R&D, marketing.
- Political situation and stability.

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- Operations shall be performed within specifically defined areas of adequate size.
- There should be procedures for -
  - Receipt, identification, storage, withholding, QC sampling.
  - Holding rejected components.
  - Storage of in-process materials.
  - Manufacturing and processing operations.

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- Packing and labelling operations.
- Quarantine storage before release of drug products.
- Storage of drug products after release; and
- Control and laboratory operations.

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- The facility shall also consider for aseptic processing
  - The following attributes are required for aseptic processing:
    - Floors, walls, ceilings should be of **smooth**, **hard surfaces** that are easily **cleanable**.
    - Equipped with temperature and humidity **controls**.
    - An air supply filtered through **HEPA** filters under **positive pressure** is provided.

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- A system for monitoring environmental conditions is in place.
- There is a system for cleaning and disinfecting the room and equipment to produce aseptic conditions; and
- A system for maintaining any equipment used to control the aseptic conditions.

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Lighting

- Adequate light shall be provided in all areas 30-50 foot-candles to ensure worker's comfort and ability to perform efficiently and effectively;

- 100 foot candles may be required in some area - e.g. inspection of filled vials.

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Heating, ventilation, and air conditioning (HVAC)

- Adequate ventilation is required in all areas.
- Equipment for adequate control over air pressure, MOs, dust, humidity, temperature shall be provided.
- When appropriate, air supplied to production areas should be filtered to avoid any possibility of contamination or cross - contamination.
- Air-handling systems for all areas shall be provided.

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Plumbing

- Potable water, meeting drinking water standard shall be supplied under continuous positive pressure in a plumbing system free of defects that would contribute contamination to any product.

- Drains shall be of adequate size.

- Where connected directly to a sewer, shall be provided with an air break or other mechanical device to prevent back-siphonage.

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Sewage and refuse

- Sewage, trash, and other refuse in and from the building and immediate premises shall be disposed of in a safe and sanitary manner.

- Disposals include: product disposal (separate from its packaging), printed packaging disposal, and general trash and sewage.

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Washing and toilet facilities

- Adequate washing facilities shall be provided including:
    - Hot and cold water
    - Soap or detergent
    - Air dryers or single-service towels, and
    - Clean toilet facilities; easily accessible to working areas.
- Lavatories and lockers shall be provided.

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Sanitation

- Any building shall be maintained in a clean and sanitary condition free of infestation by rodents, birds, insects and other vermin (other than lab animals).

- There shall be written procedures assigning responsibility for sanitarian, cleaning schedules, methods, equipment and materials to be used in cleaning the buildings and facilities.

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- There shall be written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents and cleaning and sanitizing agents.
- Procedures shall be designed to prevent contamination of equipment, components, dry products, etc.
- Sanitation procedures shall apply to work performed by contractors or others.

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Maintenance

- Any building used for the manufacture, processing, packing or holding of drug product shall be maintained in a good state of repair.

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4. Equipment

- Equipment should be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for cleaning and maintenance.

- Equipment construction

    - The surfaces that contact components, in-process materials, or drug products should not be reactive.

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- Automatic, mechanical and electronic equipment
- Filters for liquid filtration used as a part of the manufacture, processing, or packing of injectable drug products intended for human use must not release fibers into such products.

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5. Control of components and drug product containers and closures

- General requirements
- Receipt and storage of untested components and drug product containers and closures
    - Upon receipt each container of components must be visually examined for appropriate labeling and any damage or contamination.

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- Testing and approval or rejection of components and drug product containers and closures.
    - Each lot of components shall be withheld from use until it has been sampled, tested, and released by the quality control unit.
- Use of approved components and drug product containers and closures must be rotated to assure that the oldest approved stock is used first.
- Re-testing of approved components and drug product containers and closures after storage for a long period of time or after exposure to the atmosphere.
- Rejected components and drug product containers and closures should be identified and controlled under a quarantine system.

6. Production and process controls

- Written Procedures and deviations
    - Written procedures for production and process control must be written and followed.
    - All actions must be documented at the time of performance.
- Charge-in of components
    - Written production and control procedures must be followed.

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- Calculation of yield
    - Should be determined at the completion of each appropriate phase of manufacturing, processing, packaging, or holding.
- Equipment identification
    - Major equipment should be identified by a distinctive identification that shall be recorded in the batch production record to indicate the specific equipment used.

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- Sampling and Testing of in-process materials and drug products
    - To assure batch uniformity and integrity, it is necessary to write and follow procedures that describe the in-process controls and tests or examinations that will be conducted on samples taken according to procedure.
- Time limitations on production
    - When appropriate, time limits should be established for the completion of each phase of production.

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- Control of microbiological contamination
  - To prevent the growth of objectionable microorganisms in products
- Reprocessing
  - Written procedures
  - Reprocessing must not be performed without the review and approval of the quality control unit.

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7. Packaging and labeling control

- Materials examination and usage criteria
- Labelling issuance
- Packaging and labelling operations
- Tamper-resistant packaging requirements for OTC human drug products
- Drug product inspection
- Expiration dating

8. Holding and distribution

- Warehousing procedures
    - Quarantine of drug products
    - Storage of drug products
- Distribution Procedures

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9. Laboratory controls

- All actions must be documented at the time of performance and any deviation must be recorded and justified.
- Testing and release for distribution
- Stability testing

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- Special testing requirements
  - Sterile and/or pyrogen free
  - Ophthalmic ointment
  - Controlled-release dosage form
- Reserve samples
  - Representative of each lot or of each shipment of API/drug product must be retained

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10. Production management

- Personnel
- Training
- General facilities
- Cost
- Space Allocation
- Environmental Factors
- Materials, lighting, air conditioning specifications
- Dust collection and cross-contamination

11. Inventories

- Inventories are classified as follows:
  - **Materials**: chemicals (as active ingredients, excipients), finishing supplies (as containers, labels, caps, etc.)
  - **Components**: parts of sub-assemblies needed for the final assembly of the end product (e.g. bulk tablets awaiting packaging).
  - **Work-in-process:** materials and components on which work is being done.
  - **Finished goods:** sealable items, samples or other promotional items held in inventory awaiting customer order or made for specific customers.

Other areas of GMP

- Records and Reports
- Returned and Salvaged Drug Products
- Repackaging and Relabeling
- Inspection Procedure for Compliance
- Recalls and CGMPs
- Controlled Substances Safeguards
- Bulk Pharmaceutical Chemicals